Original article

Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis: A double-blind, placebo-controlled randomized trial

Fadıl Ozturk, MD,[a] Arzu Bakirtas, MD,[b] Fikret Ileri, MD,[c] and Ipek Turktas, MD[b] *Samsun and Ankara, Turkey*

Background: The place of systemic corticosteroids in the treatment of children with chronic rhinosinusitis (CRS) remains unclear.

Objective: We sought to assess the effectiveness and tolerability of oral methylprednisolone as an anti-inflammatory adjunct in the treatment of CRS in children.

Methods: Forty-eight children (age, 6-17 years) with clinically and radiologically proved CRS were included. Patients were randomly assigned to either oral amoxicillin/clavulanate (AMX/C) and methylprednisolone or AMX/C and placebo twice daily for 30 days. Oral methylprednisolone was administered for the first 15 days with a tapering schedule. Primary parameters were mean change in symptom and sinus computed tomographic (CT) scan scores after treatment. Secondary study parameters were mean changes in individual symptom scores after treatment, relapse rate, and tolerability.

Results: Forty-five patients completed the study: 22 received AMX/C and methylprednisolone, and 23 received AMX/C and placebo. Both groups demonstrated significant improvements in symptom and sinus CT scores when comparing baseline values with end-of-treatment values ($P < .001$). Methylprednisolone as an adjunct was significantly more effective than placebo in reducing CT scores ($P = .004$), total rhinosinusitis symptoms ($P = .001$), and individual symptoms of nasal obstruction ($P = .001$), postnasal discharge ($P = .007$), and cough ($P = .009$). At the end of treatment, 48% of the children in the placebo group still had abnormal findings on CT scans versus 14% in the methylprednisolone group ($P = .013$). Therapy-related adverse events were not different between groups. Although insignificant, the incidence of clinical relapses was also less in the methylprednisolone group (25%) compared with that in the placebo group (43%, $P = .137$).

Conclusion: Oral methylprednisolone is well tolerated and provides added benefit to treatment with antibiotics for children with CRS. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Chronic rhinosinusitis, methylprednisolone, computed tomographic scan*

Chronic rhinosinusitis (CRS) is an intractable inflammatory disease of the sinonasal mucosa, but it is not a simple chronic infectious disease. Although the exact pathophysiology is not clear, various factors, including microorganisms, allergic and nonallergic immunologic inflammation, and noninfectious, non-immunologic causes, can initiate CRS.[1] It has a marked negative effect on the quality of life of both patients and their families. It can also infrequently lead to serious suppurative complications, such as ophthalmitis, meningitis, brain abscess, or osteomyelitis. In children it is thought to be generally a medically treatable disease, and because of the small role of anatomic abnormalities, surgery is not often required.[2,3] However, evidence-based guidelines for safe and effective medical treatment have not been established.

Although most patients with acute rhinosinusitis are currently treated with antibiotics, they are only partially or transiently effective in patients with CRS. Symptoms might not always improve, and inflammatory mucosal thickening often persists despite treatment with antibiotics. This is an argument for the use of corticosteroids to control the inflammatory response.[4,5] Few studies have suggested that intranasal topical corticosteroids as an adjunct to oral antibiotic therapy are effective in decreasing the subjective measures of acute rhinosinusitis and CRS.[6-8] However, the place of systemic corticosteroids in the treatment of children with CRS remains unclear. Although it is thought that their anti-inflammatory effects can be beneficial in theory, their potential systemic side effects cause concern.

We aimed to examine the efficacy and tolerability of oral methylprednisolone in children and adolescents with CRS in a prospective, randomized, double-blind, placebo-controlled study. We also investigated the effects of oral methylprednisolone on the recurrence of CRS symptoms.

METHODS

Patients

Patients were recruited from the pediatric allergy and ear, nose, and throat outpatient clinics of 2 university hospitals in the same country. Because there is no similar study on the treatment of children with CRS with methylprednisolone, we used an estimate of treatment success for the calculation of sample size. We estimated that children treated with methylprednisolone and placebo will achieve a success rate of 90% and 50%, respectively. A sample size of 20 patients was found for each group, with 80% power and an α value of .05 by using the MINITAB 15 package program (Minitab, Inc, State College, Pa).

The diagnosis of CRS was made on the basis of sinonasal symptoms and signs present for a period of more than 3 months in the presence of abnormalities

From [a]the Department of Pediatrics, Division of Pediatric Allergy and Clinical Immunology, Ondokuz Mayis University Faculty of Medicine, Samsun, and [b]the Department of Pediatrics, Division of Pediatric Allergy and Asthma, and [c]the Department of Otorhinolaryngology, Gazi University Faculty of Medicine, Ankara.

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Reprint requests: Fadıl Ozturk, MD, Ondokuz Mayis University, Faculty of Medicine, Division of Pediatric Allergy and Clinical Immunology, 55200 Samsun, Turkey. E-mail: fadil@doctor.com.

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Abbreviations used
AMX/C: Amoxicillin/clavulanate
CRS: Chronic rhinosinusitis
CT: Computed tomography
VAS: Visual analog scale

on coronal sinus computed tomographic (CT) scans.[1] All patients presented with nasal purulence, postnasal purulence, or both and 1 or more of the following symptoms: nasal obstruction, cough, halitosis, headache, or facial pain/pressure. They had multiple courses (each 10-14 days, >3 courses) of antimicrobial treatment with at least 2 or more of the following broad-spectrum antibiotics before entry into the study: amoxicillin-clavulanic acid, second-generation cephalasporins (mostly cefuroxime), or clarithromycin. Patients were excluded if they had used systemic corticosteroids in the last 2 months before the study or systemic antibiotics and inhaler or intranasal corticosteroids in the last 4 weeks before the study or if they had other respiratory tract disorders (cystic fibrosis, ciliary dyskinesia, nasal polyps, large adenoids, and asthma), immune deficiency, systemic disease, gastroesophageal reflux, aspirin sensitivity, and acquired or congenital sinonasal abnormalities or a contraindication to corticosteroid use. Patients known with allergic rhinitis were also included if they also showed purulent rhinorrhea, postnasal purulence, or both, signs unlikely to be caused by allergic rhinitis only. Patients with pollen-induced rhinitis were excluded if they were seen during the pollen season. Our national and institutional ethics committees approved the study protocol, and informed consent was obtained from the parents of all participating patients.

Symptom scores

Rhinosinusitis symptoms were assessed by the patients and their parents with the use of a visual analog scale (VAS) rating symptom from 0 (none) to 10 (most severe). The following 6 symptoms were scored: purulent nasal discharge, nasal obstruction, postnasal drainage, halitosis, cough, and facial pain or headache. A total of 60 points was thus possible.

CT scanning

A coronal sinus CT scan was performed on all subjects before and at the end of treatment. The scans were evaluated and scored according to the Lund-Mackay[9] staging system. Each of the sinuses and ostiomeatal units were evaluated and scored separately. The scores for each sinus range from 0 to 2 (0, no abnormality; 1, mucosal thickening; 2, opacification; 0, ostiomeatal complex unobstructed; and 2, ostiomeatal complex obstructed). The total score for 2 sides was calculated by adding all individual scores (maximum, 24 points). Patients were required to have a combined sinus CT scan score of 5 points or greater to be included in the study. All CT scans were evaluated by an ear, nose, and throat specialist (F. I.) experienced in interpreting sinus CT scans. He was blind with respect to both treatment and sequence.

Skin prick tests

Allergen skin tests were performed with a panel of the 30 most common aeroallergens (Stallergenes, Antony, France) by using a standard prick method. A test result was considered positive if the mean wheal diameter produced by the allergens was at least 3 mm larger than that induced by the negative control.

Peripheral eosinophil count

Peripheral blood samples were analyzed for complete blood cell counts and differentials. A baseline absolute eosinophil count was calculated from the automated analysis before the start of methylprednisolone treatment.

Interventions

Patients enrolled in the study were given either oral amoxicillin/clavulanate (AMX/C) and methylprednisolone (methylprednisolone group) or AMX/C and placebo (placebo group) twice daily by using a random allocation chart based on a table of random numbers. Randomization assignments were kept in sealed envelopes. The randomization code was kept by the nursing staff in the pediatric allergy department. Oral AMX/C was administered at 45/6.4 mg/kg/d (maximum, 2000/285 mg/d) for 30 days for both groups. Oral methylprednisolone was administered for the first 15 days according to the following schedule: 1 mg/kg/d (maximum, 40 mg/d) for 10 days, 0.75 mg/kg/d for 2 days, 0.5 mg/kg/d for 2 days, and 0.25 mg/kg/d for 1 day. Daily methylprednisolone doses were rounded up to the nearest 4 mg.

Placebo tablets contained lactose and were of same size and color as methylprednisolone tablets (16 mg per tablet). Placebo and methylprednisolone tablets were dispensed in identical packets containing a minimum of 20 tablets each.

Compliance

We assessed compliance in 2 ways: parental supervision of the child while taking medication and counting the number of pills left at the second and fourth weeks of treatment.

Clinical recovery and relapse

We defined a total VAS score of zero as complete clinical recovery. Clinically significant improvement (also referred as good results in some published articles[8,10]) was defined as a total VAS score of 6 or less provided that any individual sinonasal VAS score was 2 or less.

Relapse was defined as the recurrence of sinonasal symptoms (nasal purulence, postnasal purulence, or both and ≥1 of the following symptoms: nasal obstruction, cough, halitosis, headache, or facial pain/pressure) for more than 2 months.[8] Recurrence of symptoms was monitored in each patient by means of telephone follow-up for 6 months after the end of treatment.

Tolerability

Tolerability was evaluated by means of medical history, physical examination, and measurement of adverse events. Hypertension, edema, weight gain, increase in appetite, gastrointestinal disturbances, nervousness, agitation, psychosis, headache, mood swings, delirium, euphoria, moon face, skin atrophy, bruising, hyperpigmentation, muscle weakness, joint pain, and allergic reactions were defined as clinically significant adverse events.

Outcome measures

Primary study parameters were the mean change in total symptom and coronal CT scores after treatment. Secondary study parameters were mean changes in individual symptom scores after treatment, relapse rate, and tolerability.

Statistical analysis

Results are reported as means ± SDs. Comparison in continuous demographic and disease variables between the start and end of the study within each group was made by means of paired *t* test and between groups by means of 2-sample *t* testing. Analysis was made with the Mann-Whitney test when data were not normally distributed or the variances of the data were not homogeneous. Categorical data were analyzed by using the χ^2 or Fisher exact tests.

Data were analyzed by using the Statistical Package for the Social Sciences, version 17.0 software (SPSS, Inc, Chicago, Ill). A P value of less than .05 was considered statistically significant.

RESULTS

Forty-eight patients (16 girls) were randomized, and 45 (94%) completed the study. Patients withdrew from the study for the following reasons: protocol deviations (2 [1 in the methylprednisolone group and 1 in the placebo group]) and unpalatability (1

TABLE I. Baseline characteristics of patients

	MP group (n = 22)	Placebo group (n = 23)	*P* value
Age (y [SD])	8.5 (2.9)	8.0 (2.3)	NS
Male/female ratio	14/8	15/8	NS
Weight (kg [SD])	28.4 (11.7)	26.3 (7.7)	NS
Duration of symptoms (mo [SD])	16.8 (17.1)	20.5 (13.5)	NS
Smoking in household, no. (%)	6 (27)	7 (30)	NS
Atopy, no. (%)	8 (36)	10 (43)	NS
Blood eosinophil count (SD)	274 (183)	322 (247)	NS
Total symptom score (SD)	35.1 (8.2)	36.5 (6.5)	NS
Total CT scan score (SD)	12.8 (5.3)	11.2 (4.5)	NS

All parameters were insignificant between the groups.
MP, Methylprednisolone; *NS*, not significant.

TABLE II. CT scan scores of patients with CRS before and after treatment

	Before treatment		After treatment	
Score	MP group (n = 22)	Placebo group (n = 23)	MP group (n = 22)	Placebo group (n = 23)
0	0	0	13	6
1-2	0	0	6	6
3-4	0	0	2	2
5-9	8	10	0	6
10-14	5	9	1	3
15-19	5	3	0	0
≥20	4	1	0	0

MP, Methylprednisolone.

in the methylprednisolone group). All other patients were compliant to medications checked at the second and fourth weeks of treatment by counting the remaining pills. Twenty-two patients received methylprednisolone and 23 patients received placebo in addition to AMX/C. The mean ± SD age of the patients was 8.2 ± 2.6 years (median, 7 years), with a range of 6 to 17 years. Of the 45 patients, 18 (40%) were classified as atopic on the basis of skin prick test responses: 14 had positive skin test responses for perennial aeroallergens (12 to house dust mites and 2 to house dust mites and cockroach), 3 for seasonal aeroallergens (pollens), and 1 for house dust mites and pollens. The baseline characteristics of both groups are shown in Table I. There were no statistical differences between the 2 groups concerning all baseline characteristics, including age, sex, atopy, smoking in the household, peripheral eosinophil count, symptoms, or CT scores. The most common symptoms were postnasal discharge (96%), cough (93%), nasal obstruction (91%), purulent rhinorrhea (78%), and halitosis (78%). Headache or facial pain was less frequent (64%) and less severe.

The mean ± SD baseline total symptom score in the methylprednisolone group was 35.1 ± 8.2, and it was 36.5 ± 6.5 in the placebo group. Median baseline symptom scores for all patients were as follows: cough, 8; purulent nasal discharge, 7; nasal obstruction, 7; purulent postnasal discharge, 7; halitosis, 5; and facial pain or headache, 4 (scale, 0-10 points).

Each patient included in the study had a combined sinus CT scan score of 5 points or greater. The mean ± SD baseline CT scan score in the placebo group was 11.2 ± 4.5, and it was 12.8 ± 5.3 in the methylprednisolone group. The baseline and 30-day CT scan scores of both groups are shown in Table II.

TABLE III. Baseline and posttreatment mean symptom and CT scan scores and mean change from baseline in symptom and CT scan scores

Parameter	MP group (n = 22)	Placebo group (n = 23)	*P* value*
Total symptom score			
Baseline (SD)	35.1 (8.2)	36.5 (6.5)	
After treatment (SD)	3.0 (2.9)	15.2 (12.5)	
Mean change (SD [%])	−32.1 (9.1 [91])	−21.3 (11.1 [58])	.001
P value†	<.001	<.001	
Nasal discharge			
Baseline (SD)	5.7 (3.6)	5.9 (3.6)	
After treatment (SD)	2.1 (1.8)	2.3 (2.7)	
Mean change (SD [%])	−3.6 (3.0 [63])	−3.6 (3.2 [61])	NS
P value†	<.001	<.001	
Nasal obstruction			
Baseline (SD)	6.4 (3.0)	7.0 (2.3)	
After treatment (SD)	0.3 (0.6)	3.8 (2.9)	
Mean change (SD [%])	−6.1 (2.9 [95])	−3.1 (2.8 [44])	.001
P value†	<.001	<.001	
Postnasal discharge			
Baseline (SD)	7.2 (2.6)	6.8 (2.5)	
After treatment (SD)	0.4 (0.7)	2.3 (2.6)	
Mean change (SD [%])	−6.8 (2.7 [94])	−4.5 (2.8 [66])	.007
P value†	<.001	<.001	
Halitosis			
Baseline (SD)	5.0 (3.8)	5.3 (3.3)	
After treatment (SD)	0.4 (0.7)	2.0 (2.2)	
Mean change (SD [%])	−4.5 (3.5 [90])	−3.2 (3.9 [60])	NS
P value†	<.001	.001	
Headache/facial pain			
Baseline (SD)	3.1 (3.2)	4.3 (3.8)	
After treatment (SD)	0.5 (1.2)	1.8 (2.8)	
Mean change (SD [%])	−2.6 (2.9 [83])	−2.5 (3.0 [58])	NS
P value†	<.001	.001	
Cough			
Baseline (SD)	7.4 (2.5)	7.0 (3.0)	
After treatment (SD)	0.7 (1.4)	2.8 (2.7)	
Mean change (SD [%])	−6.6 (2.6 [89])	−4.1 (3.2 [58])	.009
P value†	<.001	<.001	
CT score			
Baseline (SD)	12.8 (5.3)	11.2 (4.5)	
After treatment (SD)	1.2 (2.8)	4.1 (4.0)	
Mean change (SD [%])	−11.5 (5.4 [90])	−7.0 (4.3 [63])	.004
P value	<.001	<.001	

MP, Methylprednisolone; *NS*, not significant.
*Methylprednisolone versus placebo.
†Intragroup (day 0 vs day 30).

Both the methylprednisolone and placebo group patients had significant improvement in mean total symptoms ($P < .001$) and sinus CT scores ($P < .001$) when comparing baseline values with end-of-treatment values (Table III). Methylprednisolone was consistently and significantly more effective than placebo in reducing total ($P = .001$) and individual rhinosinusitis symptom scores of nasal obstruction ($P = .001$), postnasal discharge ($P = .007$), and cough ($P = .009$) but not nasal discharge ($P = .127$), halitosis ($P = .371$), and headache or facial pain ($P = .953$, Table III and Fig 1).

The achieved reductions in CT scores were also significantly greater with methylprednisolone than with placebo ($P = .004$, Table III and Fig 1).

At the end of treatment, 19 (86%) of 22 methylprednisolone-treated and 12 (52%) of 23 placebo-treated patients had no

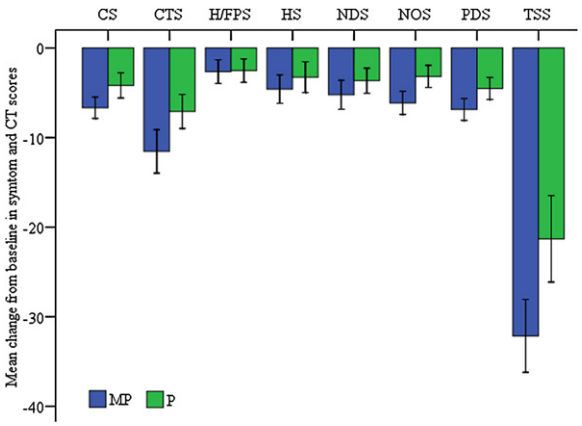

FIG 1. Mean change from baseline in symptom and CT scan scores. *Columns* and *error bars* represent means and 95% CIs. *CS*, Cough score (P = .009); *CTS*, CT scan score (P = .004); *H/FPS*, headache or facial pain score (P > .05); *HS*, halitosis score (P > .05); *MP*, methylprednisolone; *NDS*, nasal discharge score (P > .05); *NOS*, nasal obstruction score (P = .001); *P*, placebo; *PDS*, postnasal discharge score (P = .007); *TSS*, total symptom score (P = .001).

residual disease when a cutoff point of a Lund-Mackay score of 2 or less was used to define a normal CT scan (Table II). This difference was also statistically significant (P = .02).

Complete clinical recovery and clinically significant improvement were found in 24 (53%) patients (17 in the methylprednisolone group and 7 in the placebo group) and were significantly more frequent in the methylprednisolone group compared with the placebo group (P = .005).

At telephone follow-up, the incidence of clinical relapse was also less in the methylprednisolone group, although differences were not significant (P = .137): 25% (4/16) of the methylprednisolone group compared with 43% (3/7) of the placebo group.

No clinically significant adverse events were reported. Twenty-seven parents (16 in the methylprednisolone group and 11 in the placebo group) reported that their children's appetite and weight increased after treatment. At the end of the treatment, the mean ± SD changes in patients' weights from baseline were 0.42 ± 0.26 kg in the methylprednisolone group versus 0.27 ± 0.30 kg in the placebo group. The difference was not significant (P = .08).

DISCUSSION

This is the first randomized, double-blind, placebo-controlled study evaluating the efficacy and tolerability of an oral corticosteroid in combination with antibiotics in children and adolescents with CRS without nasal polyposis. The present study showed that oral methylprednisolone as an adjunct to recommended antibiotherapy was significantly more effective than placebo not only in reducing total rhinosinusitis symptoms but also CT scores and the most bothersome individual symptoms of CRS, which are nasal obstruction, postnasal discharge, and cough.

There are no previously published placebo-controlled data showing the efficacy of oral corticosteroids in patients with CRS without nasal polyposis either before or after surgery. Few published experiences with systemic corticosteroid use in patients with CRS are in the form of small, uncontrolled case series. Therefore it is hard to compare our results with those described in literature. There is 1 retrospective analysis reported by Subramanian et al.[11] They reported results of 40 patients (average age, 48.2 years; range, 11-81 years) with chronic sinusitis treated with an intensive medical regimen, including oral prednisone for 10 days (20 mg twice daily for 5 days followed by 20 mg once daily for 5 days). Antibiotics were administered for 4 to 8 weeks. Similar to our results, this retrospective data analysis also showed that systemic corticosteroid treatment was effective in improving both symptom and CT scores of patients with CRS.

In our study we used both an objective (paranasal sinus CT scan scores) and a subjective (VAS scores of the most common symptoms) parameter to measure the efficacy of oral methylprednisolone in children and adolescents with CRS. Currently, a coronal CT scan is the imaging technique of choice to study paranasal sinuses.[12] The paranasal CT scan reliably demonstrates CRS when present with a sensitivity of more than 80%.[13] The Lund-Mackay[9] system is also widely used around the world for radiographic staging of CRS on CT. This scoring system is recommended because of its high degree of interobserver agreement and ease of learning by nonradiologists.[14] However, the presence of soft tissue abnormalities in children who have no symptoms of sinus disease is an important issue. In a group of children with no sinusitis symptoms but who had cranial CT scans for other reasons, Hill et al[15] reported a mean raw Lund-Mackay score of 2.1 and scaled score of 2.8 (based on number of sinuses actually pneumatized). The authors concluded that a score of 4 or greater is likely to represent true sinus disease rather than an incidental finding. For this reason, in the present study patients were required to have a combined sinus CT scan score of 5 or more points in addition to rhinosinusitis symptoms. Despite the fact that 10 (5 in the methylprednisolone group and 5 in the placebo group) of 45 patients did not have pneumatized frontal sinuses, the mean ± SD CT scan scores (12.0 ± 4.9) of our patients were compatible with those of patients with severe sinus disease.

Glucocorticosteroids are well-established anti-inflammatory agents. It has been shown that in CRS nasal mucosa culture, corticosteroids reduce the production of many inflammatory molecules, such as IL-5, IL-8, and GM-CSF.[16] It is also well known that corticosteroids are currently the most effective drugs in the treatment of eosinophilic inflammation in airways mucosa as in asthma. Although CRS in children differs from that in adults histopathologically,[17] studies have demonstrated that the mucosa in patients with pediatric CRS shows increased eosinophil and lymphocyte counts compared with those seen in normal mucosa.[18,19] Therefore corticosteroids might also help to reduce eosinophilic inflammation in the sinus tissues.

A few randomized studies have suggested that intranasal topical corticosteroids as an adjunct to oral antibiotic therapy are effective in decreasing subjective measures of acute and CRS.[6-8] The mechanism of intranasal corticosteroids in CRS treatment is not fully understood. There is no study that compared the efficacy of intranasal and systemic corticosteroids. Although it is not irrational to expect that systemic corticosteroids are able to reach the diseased area more properly than a local corticosteroid spray, it might be a good idea to do a follow-up study comparing systemic with topical corticosteroid treatment in children with CRS without nasal polyposis.

Although not proved, it is suggested that there is a connection between allergy and CRS in children.[3,20] In our study there were no statistical differences between the 2 groups concerning atopy or baseline peripheral eosinophil counts. Although Newman et al[21] have suggested that the presence of allergy and peripheral eosinophilia (≥300/mL) in adult patients with CRS indicates a high likelihood of extensive disease, we did not find any

correlation among atopy, peripheral eosinophil counts, and disease severity. Furthermore, neither we nor other researchers[11] found any correlation between the response to CRS treatment and allergy parameters, such as atopic sensitization and peripheral eosinophil counts.

In our study there was still evidence of residual disease on CT scans after treatment in 48% of the placebo group and 14% of the methylprednisolone group when a cutoff point of a Lund-Mackay score of 2 or less was used to define a normal CT scan. These results suggest that antibiotics alone were not sufficient to resolve mucosal inflammation in a substantial number of children with CRS. On the other hand, in the methylprednisolone group a nonatopic 15-year-old girl with very extensive chronic sinus disease (baseline CT scan score, 15) showed an insignificant improvement both radiologically (CT scan score after treatment, 12) and clinically after treatment with oral methylprednisolone. An explanation for this failure might be irreversible inflammatory mucosal changes completely resistant to corticosteroids.[22,23] Differential responses to corticosteroids and antibiotics as a function of the infecting microorganisms might be another possible explanation.[24] In any case, CRS is still an unresolved disease with many heterogeneities and subtypes. It is not a pure eosinophilic disease; rather, it involves a wide range of inflammatory cells. Not only the type of inflammatory cells but also the intensity of the cellular infiltrate might be variable among patients with CRS, which could be the reason for different response profiles of patients to corticosteroids.[25]

In our study both systemic corticosteroid and antibiotic treatments were well tolerated. Although an increase in appetite and weight gain, the only reported adverse event, was more common in the methylprednisolone group (73% vs 48%), mean changes from baseline in the weights of patients between groups were not significant.

Our study has some limitations. We did not perform sinus puncture and microbial culture for bacteria, virus, or fungi. Therefore we could not determine whether unresponsive cases were infected by resistant strains. However, our study is a randomized one, and hence we assume that if there were resistant strains, they were probably distributed alike in both the placebo and MP groups. Second, we treated all patients with 45/6.4 mg/kg/d oral AMX/C (maximum, 2000/285 mg/d), which is less than recommended by some experts, but this is the standard recommended antibiotherapy and dose for patients with CRS.[26] Third, we monitored the relapse of CRS only with recurrence of symptoms by telephone call and did not perform a follow-up paranasal CT scan.

In summary, treatment with oral methylprednisolone as an adjunct to standard antibiotic treatment is well tolerated and helpful in improving symptom and CT scores in both atopic and nonatopic children with radiographically confirmed CRS. Our study also suggests that oral methylprednisolone given for 15 days in combination with standard antibiotic treatment might reduce the probability of recurrence in the medium term.

Clinical implications: Oral methylprednisolone as an adjunct to antibiotic therapy reduces both total rhinosinusitis symptoms and CT scan scores in children and adolescents with CRS without nasal polyposis.

REFERENCES

1. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol 2004;114:155-212.
2. Parsons DS. Chronic sinusitis. A medical or surgical disease? Otolaryngol Clin North Am 1996;29:1-9.
3. Wu AW, Shapiro NL, Bhattacharyya N. Chronic rhinosinusitis in children: what are the treatment options? Immunol Allergy Clin North Am 2009;29: 705-17.
4. Hamilos DL. Chronic sinusitis. J Allergy Clin Immunol 2000;106:213-27.
5. Desrosiers MY, Kilty SJ. Treatment alternatives for chronic rhinosinusitis persisting after ESS: what to do when antibiotics, steroids and surgery fail. Rhinology 2008;46:3-14.
6. Meltzer EO, Orgel HA, Backhaus JW, Busse WW, Druce HM, Metzger WJ, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. J Allergy Clin Immunol 1993;92:812-23.
7. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Ann Allergy Asthma Immunol 1997;786:598-601.
8. Dijkstra MD, Ebbens FA, Poublon RM, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clin Exp Allergy 2004;34:1395-400.
9. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology 1993;31:183-4.
10. Danielsen A, Olofsson J. Endoscopic endonasal sinus surgery. A long-term follow-up study. Acta Otolaryngol 1996;116:611-9.
11. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. Am J Rhinol 2002;16:303-12.
12. Triulzi F, Zirpoli S. Imaging techniques in the diagnosis and management of rhinosinusitis in children. Pediatr Allergy Immunol 2007;18:46-9.
13. Isaacson G. Sinusitis in childhood. Pediatr Clin North Am 1996;43:1297-318.
14. Metson R, Gliklich RE, Stankiewicz JA, Kennedy DW, Duncavage JA, Hoffman SR, et al. Comparison of sinus computed tomography staging systems. Otolaryngol Head Neck Surg 1997;117:372-9.
15. Hill M, Bhattacharyya N, Hall TR, Lufkin R, Shapiro NL. Incidental paranasal sinus imaging abnormalities and the normal Lund score in children. Otolaryngol Head Neck Surg 2004;130:171-5.
16. Wallwork B, Coman W, Feron F, Mackay-Sim A, Cervin A. Clarithromycin and prednisolone inhibit cytokine production in chronic rhinosinusitis. Laryngoscope 2002;112:1827-30.
17. Chan KH, Abzug MJ, Coffinet L, Simoes EA, Cool C, Liu AH. Chronic rhinosinusitis in young children differs from adults: a histopathology study. J Pediatr 2004; 144:206-12.
18. Baroody FM, Hughes CA, McDowell P, Hruban R, Zinreich SJ, Naclerio RM. Eosinophilia in chronic childhood sinusitis. Arch Otolaryngol Head Neck Surg 1995; 121:1396-402.
19. Driscoll PV, Naclerio RM, Baroody FM. CD4+ lymphocytes are increased in the sinus mucosa of children with chronic sinusitis. Arch Otolaryngol Head Neck Surg 1996;122:1071-6.
20. Zacharek MA, Krouse JH. The role of allergy in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg 2003;11:196-200.
21. Newman LJ, Platts-Mills TAE, Philips CD, Hazen KC, Gross CW. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. JAMA 1994;271:363-7.
22. Mullol J, Obando A, Pujols L, Alobid I. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. Immunol Allergy Clin North Am 2009;29: 657-68.
23. Pujols L, Mullol J, Picado C. Importance of glucocorticoid receptors in upper and lower airways. Front Biosci 2010;15:789-800.
24. Weinberger M. Should corticosteroids be used for first-time young wheezers? J Allergy Clin Immunol 2007;119:567-9.
25. van Drunen CM, Reinartz S, Wigman J, Fokkens WJ. Inflammation in chronic rhinosinusitis and nasal polyposis. Immunol Allergy Clin North Am 2009;29: 621-9.
26. Schleiss MR. Nelson Textbook of Pediatrics. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Principles of antibacterial therapy. 18th ed. Philadelphia: Saunders Elsevier; 2007. p. 1110-22.